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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DEFENDANT VYSIS' MEMORANDUM OF CONTENTIONS OF FACT AND LAW

Date: February 4, 2002
Time: 10:30 a.m.
Courtroom: 1

Pursuant to Local Rule 16.1(f), defendant Vysis, Inc. ("Vysis") hereby submits its Memorandum of Contentions of Fact and Law. This Memorandum also sets forth Vysis' pretrial disclosures as required by Fed. R. Civ. P. 26(a)(3).

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INTRODUCTION

1. The invention disclosed and claimed in U.S. Patent No. 5,750,338 ("the '338 patent") has proven to be critical to the development of sensitive, automated, nucleic-acid-based detection systems of the sort required, for example, to screen the nation's blood supply for dangerous viral pathogens such as HIV and Hepatitis C. While the development of the so-called "polymerase chain reaction" ("PCR") and other such *in vitro* techniques for the amplification of polynucleotides was originally believed to provide the ability to detect target polynucleotides present in very small amounts in complex samples, this has not proven to be the case. The presence of non-target polynucleotides in the sample that are amplified along with the target, and the presence in the sample of inhibitors and impurities that interfere with the amplification process, were significant problems with such first generation amplified assays. So troublesome was this aspect of these first generation assays that it has been called the "Achilles' heel" of nucleic acid amplification tests.

2. The invention of the '338 patent overcomes this "Achilles' heel" by providing for the capture of the target polynucleotide, whereby the target is substantially separated from non-target polynucleotides and other interfering substances in the sample, prior to being subjected to one of the several available *in vitro* amplification and detection processes. This combination of steps was demonstrated to be nonobvious during procurement of the '338 patent because the prior art taught away from the combination of target capture prior to amplification in nucleic acid detection assays. Additional sample handling steps, such as target capture, add mechanical complexity to automated systems and carry with them the omnipresent threat of loss of target polynucleotides present in only very small amounts. Such steps were viewed as contra-indicated in the development of highly automated and sensitive nucleic acid detection systems of the sort in which the invention of the '338 patent has found its most immediate application. Indeed, the availability of specific amplification techniques, such as PCR, at the time the invention was made, wrongly led developers of nucleic acid detection assays to believe that a preliminary target capture step was unnecessary.

3. The importance of the invention of the '338 patent is attested to by the actions of those who have appropriated it and who are now trying to circumvent the patent. Gen-Probe

Incorporated ("Gen-Probe"), a wholly owned subsidiary of a multinational Japanese drug company, Chugai Pharmaceuticals Inc. ("Chugai"), has incorporated the present invention into a highly automated, sensitive, nucleic-acid-based system for the detection of HIV and Hepatitis C in the nation's blood supply. Gen-Probe is doing so in the context of an alliance with Chiron Corporation. The patented invention is also being used in a test for the sexually transmitted diseases chlamydia and gonorrhea, marketed by Gen-Probe as its APTIMA Combo 2 assay. Gen-Probe has developed an instrument called TIGRIS to run assays using target capture and amplification. While Gen-Probe filed this declaratory judgment action seeking to invalidate the '338 patent, the depth of Gen-Probe's conviction in the merit of its current contentions must be judged in light of the fact that it has done so only after it secured a license under the '338 patent. To this day, Gen-Probe has not repudiated that license and, in fact, continues to pay royalties under the license.

4. Gen-Probe and Chiron certainly believe that the blood screening system embodying the present invention will be a huge commercial success, resulting in the payment of large royalties for use of the licensed invention. Market analysts have estimated the market potential for these products as $400-500 million per year. Moreover, both Gen-Probe and Chiron contemplate introduction of additional new products utilizing the invention, surely providing an economic motive to try to invalidate the patent. However, the underlying facts clearly demonstrate the nonobviousness and patentability of the invention. This is undoubtedly why Gen-Probe pursues its present course only under the protective umbrella of its extant license under the '338 patent.

STATEMENT OF MATERIAL FACTS

I. The Parties

A. Vysis

5. Vysis is a Delaware corporation with its principal place of business at 3100 Woodcreek Drive, Downers Grove, Illinois, 60515. Vysis is a leading Genomic Disease Management company that develops, commercializes and markets clinical products providing information critical to the evaluation and management of cancer, prenatal disorders, and other genetic diseases. Vysis was recently purchased by Abbott Laboratories, Inc., of Abbott Park, Illinois, and is operating as a wholly-owned subsidiary.

B. Gen-Probe

6. Gen-Probe is a Delaware corporation with its principal place of business at 10210 Genetic Center Drive, San Diego, California. Gen-Probe is a wholly-owned subsidiary of Chugai Pharmaceuticals, Inc.

C. The '338 Patent

7. The '338 patent is directed to diagnostic assays using the combination of target capture prior to *in vitro* amplification of a target polynucleotide, for the purpose of detecting the presence of a target polynucleotide in a biological sample. The '338 patent contains 40 claims directed to methods and kits for amplifying and detecting a target polynucleotide.

8. The inventions claimed in the '338 patent were made by four scientists: Mark L. Collins, Donald N. Halbert, Walter King, and Jonathan M. Lawrie. On December 21, 1987, those scientists filed the first of a series of patent applications claiming the combination of target capture prior to *in vitro* amplification of a target polynucleotide. That series of patent applications eventually led to issuance of the '338 patent on May 12, 1998.

D. The '338 Patent License Agreement

9. In 1999, as a condition to settling other, unrelated litigation between Gen-Probe and Vysis, Gen-Probe insisted upon receiving a license to practice the inventions claimed in the '338 patent. That license agreement allows Gen-Probe to practice the technology disclosed and claimed in the '338 patent. In return, Gen-Probe is obligated to pay Vysis a royalty of 3% of the commercial sales of each product covered by the license. Gen-Probe has not repudiated its license and instead continues to pay royalties to Vysis in order to keep the license in place. Gen-Probe has also exercised options under the license agreement to extend the license to two of its partners, Chiron and Bayer, and further arranged for a license to be granted to bioMerieux Vitek, Inc. The royalties Gen-Probe will pay under the '338 patent license are expected to greatly exceed the cost of this lawsuit. Gen-Probe has kept its license in force as "insurance" recognizing the possibility that its challenge to the '338 patent might fail.

E. Gen-Probe's HIV/HCV Assay

10. Gen-Probe, through an alliance with Chiron, has developed an assay to screen the world's blood supply for the presence of the human immunodeficiency virus and the hepatitis C virus (the "HIV/HCV assay"). That assay employs methods and is embodied in kits protected by the claims of the '338 patent.

11. Gen-Probe is distributing its HIV/HCV assay throughout the U.S. on a non-commercial basis while seeking approval from the United States Food and Drug Administration to market the HIV/HCV assay in this country. Gen-Probe is currently selling its HIV/HCV assay for profit in several foreign countries.

II. Infringement

12. Vysis does not contend and has not contended that Gen-Probe is infringing the '338 patent by virtue of making, using, or selling its HIV/HCV assay without permission. So long as Gen-Probe is licensed under the '338 patent and fulfills its obligations under that license agreement,

Gen-Probe's HIV/HCV assay does not and will not accrue liability for infringement of the '338 patent.

13. Gen-Probe's HIV/HCV assay does, however, fall within the enforceable scope of at least one claim of the '338 patent as set forth below.

A. Claim Construction

14. The Court has previously interpreted the term "amplifying" as used in the claims of the '338 patent relevant Gen-Probe's HIV/HCV assay (the "asserted claims") as literally encompassing only so-called "non-specific" amplification techniques because of the focus of the patent examples on such techniques. Vysis disagrees with that claim construction. Should the Court so allow, Vysis is prepared to make an offer of proof that the claims should be construed to encompass "specific" amplification techniques. There are, however, certain additional constructions of terms in the '338 patent claims that logically follow from at least the *ratio decidendi* of the Court's construction of the term "amplifying." Because all of the patent examples concerning target capture with amplification are so limited, the claims should be interpreted as follows:

a. The term "amplifying" as used in the asserted claims of the '338 patent must be construed as meaning *in vitro* techniques of creating many copies of the target polynucleotide. These are the only types of techniques disclosed in the '338 patent and are the only types of techniques suitable for use in detection of nucleic acids in samples. *In vivo* techniques such as "cloning," whereby DNA sequences are duplicated inside living cells, are not amplification techniques useful in detection of nucleic acids in samples and are not "amplifying" the target polynucleotide within the meaning of the '338 patent claims. Making a single copy of the target, as by reverse transcription from a target RNA, is not "amplifying" within the meaning of the claims.

b. The phrase "amplifying the target polynucleotide" must be construed to mean "*target* amplification," not only in view of the Court's decision but also in view of the plain language of the claims. Target amplification requires production of new copies of the target molecule, i.e., the copying of nucleic acid sequence information from the target. "Probe" or "signal" amplification techniques, therefore, are not within the scope of the asserted claims of the '338 patent because such

techniques do not amplify the target polynucleotide. Thus, the "target polynucleotide" is the polynucleotide in the clinical sample from which sequence information is copied during amplification.

c. The term "binds" as used in the asserted claims of the '338 patent must be construed as meaning capture of the target polynucleotide onto the support via a capture probe designed to hybridize to a sequence specific to the target polynucleotide. The term "binds" must also be construed to encompass indirect binding of the probe to the support through the action of complementary homopolymer tails.

d. The "separating" step (b) of the method claims must be construed as substantially separating the target polynucleotide from non-target polynucleotides.

B. Gen-Probe's HIV/HCV Assay Performs Each Step of the Claims of the '338 Patent[1]

15. The patented invention is most easily understood by reference to claims 7-10, 13, and 14 of the '338 patent. Claim 7 recites "A method for detecting a target polynucleotide contained in a sample comprising the steps of: (a) contacting the sample with a first support which binds to the target polynucleotide; (b) substantially separating the support and bound target polynucleotide from the sample; (c) amplifying the target polynucleotide; and (d) detecting the presence of the amplified target polynucleotide."

16. Gen-Probe's HIV/HCV test performs each of the steps recited in Claim 7 or its equivalent. First, the sample to be assayed is placed in a reaction tube and contacted with magnetic particles (the "first support") and a sequence-specific, nucleic-acid capture probe including a base sequence complementary to a base sequence in the target polynucleotide. These particles bind to the target polynucleotide via the capture probe, if the target is present in the sample. In other words, in Gen-Probe's test the magnetic particles (first support) at the time of target capture are both in contact

[1] This section also sets forth Vysis' contentions as to how, but for the '338 patent license, the claims of the '338 patent would be infringed, pursuant to Local Rule 16.1(f)(3)(e)(2) (as renumbered, Dec. 18, 2001).

with the sample and bound to the target because the capture probe binds to both the target and the magnetic particles. That step constitutes step (a) of Claim 7 or its equivalent. That the capture probe is bound to the support by complementary homopolymer tails on the probe and the support does not avoid literal infringement. This feature is described in all the examples of combined target capture and amplification in the '338 patent and constitutes at least indirect binding of the probe and target to the support.

17. Next, the magnetic particles in Gen-Probe's assay are drawn to the side of the reaction tube by magnets and then washed, to purify and concentrate targets and remove extraneous material. This action substantially separates the support and bound target polynucleotide from the remainder of the sample, thus constituting step (b) of Claim 7 or its equivalent.

18. Steps (a) and (b) of claim 7 together are commonly known as "Target Capture" because the target polynucleotide is "captured" onto a solid support which permits the target to be separated from the remainder of the sample.

19. The next step in Gen-Probe's HIV/HCV test is amplification of the target polynucleotide by Gen-Probe's Transcription-Mediated Amplification ("TMA") process. Gen-Probe's TMA technique of amplifying target nucleic acids is legally equivalent to the methods of amplification claimed in step (c) of claim 7 of the '338 patent even if the '338 patent claims are construed as being directed to non-specific amplification techniques.

20. Claim 7 also recites a step (d), "detecting the presence of the amplified target polynucleotide." Gen-Probe's HIV/HCV test includes a dual kinetic assay ("DKA") detection step after the amplification step. Accordingly, Gen-Probe's HIV/HCV test performs each of the steps recited in Claim 7 of the '338 patent or their equivalent.

21. Claim 8 of the '338 patent recites "The method of claim 7 wherein the first support is retrievable." The magnetic particles used in Gen-Probe's HIV/HCV test may be substantially dispersed within the assay medium and separated from the medium by immobilization and are, therefore, "retrievable." Indeed, one of the steps in Gen-Probe's HIV/HCV test is retrieval of the magnetic particles through immobilization by exposing them to a magnetic field. Accordingly, Gen-Probe's HIV/HCV test satisfies the additional limitation set forth in claim 8.

22. Claim 9 of the '338 patent recites "The method of claim 8 wherein the first support includes a probe which binds with the target polynucleotide." As described above, Gen-Probe's HIV/HCV assay has a first support (magnetic particles) that includes at the time of target capture a sequence-specific, nucleic-acid capture probe which binds with the target polynucleotide. Accordingly, Gen-Probe's HIV/HCV assay satisfies the additional limitation set forth in claim 9.

23. Claim 10 of the '338 patent recites "The method of claim 7 wherein the target polynucleotide is amplified with a polymerase." Gen-Probe's TMA process uses both reverse transcriptase and RNA polymerase. Accordingly, Gen-Probe's HIV/HCV test satisfies the additional limitation set forth in claim 10.

24. Claim 13 of the '338 patent recites "The method of claim 7 wherein the amplified target polynucleotide is contacted with a label." Gen-Probe's DKA technology involves contacting the amplified polynucleotide with probes containing an acridinium ester label. Accordingly, Gen-Probe's HIV/HCV test satisfies the additional limitation set forth in claim 13.

25. Claim 14 of the '338 patent recites "The method of claim 7 wherein the amplified target polynucleotide is contacted with a labeled probe." Gen-Probe's DKA technology involves contacting the amplified polynucleotide with acridinium ester-labeled DNA probes that bind to the amplified target polynucleotide. Accordingly, Gen-Probe's HIV/HCV test satisfies the additional limitation set forth in claim 14.

26. Claim 1 of the '338 patent is similar to Claim 7, but does not recite the detection step. The preamble of the claim recites "A method for amplifying a target polynucleotide contained in a sample," and then the claim sets forth three steps that comprise that method. Steps (a), (b), and (c) of Claim 7 are identical to steps (a), (b), and (c) of Claim 1, and accordingly the analysis set forth above for Claim 7 is the same for these steps of Claim 1.

27. Claim 2 of the '338 patent recites "The method of claim 1 wherein the first support is retrievable." As described with respect to Claim 8 above, the magnetic particles used in Gen-Probe's HIV/HCV test are retrievable by exposing them to a magnetic field and are retrieved by this process as part of Gen-Probe's test. Accordingly, Gen-Probe's HIV/HCV test satisfies the additional limitation set forth in claim 2.

28. Claim 3 of the '338 patent recites "The method of claim 1 wherein the first support includes a probe which binds with the target polynucleotide." As described with respect to Claim 9 above, Gen-Probe's HIV/HCV assay has a first support (magnetic particles) that includes a capture probe which binds with the target polynucleotide. Accordingly, Gen-Probe's HIV/HCV assay satisfies the additional limitation set forth in claim 3.

29. Claim 4 of the '338 patent recites "The method of claim 1 wherein the target polynucleotide is amplified with a polymerase." As described with respect to Claim 10 above, Gen-Probe's TMA process uses reverse transcriptase and RNA polymerase. Accordingly, Gen-Probe's HIV/HCV test satisfies the additional limitation set forth in claim 4.

30. Another independent claim of the '338 patent, Claim 24, recites "A kit for detecting a target polynucleotide contained in a sample comprising: (a) means for substantially separating the target polynucleotide from the sample and (b) means for amplifying the target polynucleotide." The labeling associated with Gen-Probe's assay at the time of sale refers to it as a "kit." As described above, the target capture process used in Gen-Probe's HIV/HCV test constitutes means for substantially separating the target polynucleotide from the sample which are substantially identical to the corresponding means for separating the target polynucleotide from the sample described, for example, in Example 4 of the '338 patent, or its equivalent. Moreover, Gen-Probe's TMA process is a means of amplifying the target polynucleotide which is at least equivalent to the amplification means described in the patent for reasons set forth below. Accordingly, Gen-Probe's HIV/HCV test kits contain both of the limitations of Claim 24.

31. Claim 25 recites "The kit of claim 24 wherein: (a) the means for substantially separating the target polynucleotide from the sample includes a support which binds to the target polynucleotide and (b) the means for amplifying the target polynucleotide includes a polymerase." As described above, the target capture process used in Gen-Probe's HIV/HCV test employs magnetic particles that bind to the target polynucleotide. Additionally, Gen-Probe's TMA process uses both reverse transcriptase and RNA polymerase. Accordingly, Gen-Probe's HIV/HCV test kits satisfy the added limitations of Claim 25.

C. The Amplification Step of Gen-Probe's HIV/HCV Assay is Legally Equivalent to the Amplification Techniques Claimed in the '338 Patent in the Context of the Claimed Invention

32. All nucleic acid amplification techniques have some element of non-specificity. Thus, even so-called specific amplification protocols, such as polymerase chain reaction ("PCR") amplification and Gen-Probe's TMA amplification, are non-specific to varying degrees. The degree of non-specificity of an amplification protocol depends on the conditions of amplification and the intrinsic properties of the protocol. In general, TMA is less target-specific than PCR. One of the functions performed by target capture in Gen-Probe's HIV/HCV assay is to purify the target prior to amplification, thus minimizing amplification of non-target sequences – the very function performed by target capture prior to non-specific amplification in the claimed invention.

33. Similarly, all amplification systems, whether specific or non-specific, rely on the action of enzymes that may be inhibited by materials other than the target nucleic acid in the sample. Thus, to the extent that Gen-Probe employs target capture prior to amplification to minimize the effects of amplification enzyme inhibitors, this function is necessarily also performed in connection with non-specific amplification in the claimed invention.

34. The function of Gen-Probe's TMA technique is to enable the production of a multitude of target polynucleotides from a sample that may initially contain only very few target polynucleotides. That process permits detection of the presence of a target polynucleotide that may otherwise go undetected as a result of its low concentration in a clinical sample.

35. The way TMA does so involves using oligonucleotide "primers" and an enzyme to create a double-stranded DNA molecule from a single-stranded target polynucleotide. The TMA technique, across several amplification cycles, then uses RNA polymerase to create multiple RNA molecules from that double-stranded DNA. Those RNA molecules are then detected by contacting them with a complementary labeled DNA probe.

36. The amplification techniques disclosed and claimed in the '338 patent perform substantially the same function in substantially the same way. For example, Example 5 of the '338 patent teaches using oligonucleotide "primers" and an enzyme to create a double-stranded DNA molecule from a single-stranded target polynucleotide. Example 5 then teaches the use of RNA

polymerase to create multiple RNA molecules from that double-stranded DNA. As in Gen-Probe's TMA process, those RNA molecules are detected by contacting them with a complementary labeled DNA probe.

37. Finally, the result attained by amplification in the Gen-Probe assay is to increase the amount of target nucleic acid available for detection. This is the same result obtained by amplification in the claimed invention.

38. The only difference between Gen-Probe's TMA technique and the techniques claimed in the '338 patent, as construed by the Court, is that TMA is intended to specifically amplify only the target polynucleotide whereas amplification in the claimed invention is intended to amplify whatever polynucleotides are present. This difference is not significant in the context of the patented invention. Because the target capture step disclosed and claimed in the '338 patent acts to substantially eliminate polynucleotides other than the target prior to the amplification step, both non-specific and specific amplification will result primarily in copying of the target polynucleotide in the context of the claimed invention.

39. Whether the primers used in amplification are intended to be specific (as in TMA) or intended to be non-specific (as in some embodiments of the patented invention), they function in substantially the same way: they bind to the target polynucleotide and act as the "starting point" for the enzyme that creates the double-stranded DNA molecule.

40. Although most non-specific primers do not always bind to a predetermined sequence of the target polynucleotide, this difference is inconsequential. At least some of the non-specific primers bind to the target in a sequence-specific fashion, thus initiating nucleic acid synthesis. Both techniques create an amplifiable double-stranded DNA molecule. Because the target capture step disclosed and claimed in the '338 patent acts to substantially eliminate polynucleotides other than the target prior to the amplification step, both non-specific and specific primers will bind primarily to and initiate copying primarily of the target polynucleotide in the context of the claimed invention.

41. Accordingly, the same result – creation of double-stranded DNA – is reached whether one uses "specific" primers or "non-specific" primers. One could use the "specific" primers of Gen-Probe's TMA process in place of the "random" primers of Example 5 of the '338 patent and

achieve substantially the same result. The amplification techniques of the '338 patent will work regardless of whether the primers are "specific" or "random." The '338 patent explicitly so states in Example 5 by providing that amplification may alternatively be initiated by using the sequence-specific capture probe as the primer.

III. Validity[2]

A. Novelty

42. None of the references that Gen-Probe has identified during discovery discloses each and every limitation of any of the asserted claims of the '338 patent.

43. Arsenyan et al., *Gene* 11:97-108 (1980), does not disclose amplification, detection methods, or kits. Arsenyan, a 1980 report on the isolation of rat liver 5S genes, isolated the gene by "(a) enrichment of DNA fragments carrying the genes of interest, and (b) subsequent cloning and amplification of these fragments." The "amplification" was via cloning into the *Eco*RI site of pBR322, using *E. coli* as a host.

44. Among the deficiencies of Arsenyan as an allegedly anticipatory reference, the most significant may be its failure to teach amplification within the meaning of the claims. When properly construed, the term "amplifying" as used in the claims of the '338 patent refers to *in vitro* enzymatic methods of target amplification. The cloning procedures taught by Arsenyan are *in vivo* techniques that would not be understood by those of ordinary skill in the art to be in accordance with the teachings of the '338 patent or suitable for use in assays for the detection of nucleic acids in samples. Moreover, Arsenyan does not describe or suggest the detection methods or kits specified by many of the '338 patent claims.

45. Gaubatz et al., *Biochim. Biophys. Acta* 825:175-187 (1985), does not disclose either amplifying or detecting a target polynucleotide. Gaubatz purified globin mRNA by chromatography, which was then "amplified" based on its hairpin loop structure using the

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[2] This section sets forth Vysis' contentions in response to the bases on which Gen-Probe has asserted that the claims of the '338 patent are invalid, pursuant to Local Rule 16.1(f)(3)(e)(1) (as renumbered, Dec. 18, 2001).

"displacement synthesis" method. In the first instance, the objective of Gaubatz is to prepare cDNA for *in vivo* cloning – which would not be considered by those of ordinary skill in the art to be "amplifying" in the context of the '338 patent. Further, there is no disclosure of use of this technique to detect nucleic acid targets in samples or kits.

46. To the extent that an intermediate step is undertaken in an effort to increase the concentration of the coding sequences derived from the mRNA, so-called "displacement synthesis," Gaubatz is equivocal as to whether "amplification" actually took place at all and explicitly indicates that the result of the "displacement synthesis" was not a faithful reproduction of the target messenger RNA sequences.

47. The approach proposed by Gaubatz was not a method of faithfully amplifying target DNA sequences suitable for use in a nucleic acid detection assay and does not anticipate any of the claims of the '338 patent. Further, the myriad processing steps included in the Gaubatz process (numerous organic extractions, chromatographic separations, ethanol precipitations, and polysomal preparations) render it plainly unsuitable for use in a diagnostic kit, instrumented assay, or other detection assay.

48. Powell et al., *Cell* 50:831-840 (1987), is also not directed to any technique suitable for use in nucleic acid detection assays on clinical samples or in kits. No such detection assay or kit is described. Indeed, the techniques described by Powell, which would take at least several days to complete, are wholly unsuitable for nucleic acid detection assays on clinical samples. The microgram quantities of mRNA used in the techniques (page 839, col. 1, paragraph 5) also highlight the unsuitability of the disclosed techniques in detection assays – assays where the acknowledged challenge is developing systems that are sensitive enough to detect the very minute amounts of target nucleic acid material available in the usual clinical sample.

49. Beyond the foregoing, Powell does not perform a target capture step for the purpose of enhancing the efficiency of a subsequent *in vitro* amplification step. Powell instead describes the use, in some but not all cases, of the trivial step of separating by absorption on an oligo-dT column all the cellular mRNA molecules (which have poly A tails) from associated ribosomal RNA molecules (which do not have poly A tails), which had already been separated from the cellular

milieu by other means. Indeed, Powell actually teaches away from the need to employ a target capture step prior to amplification in that a number of the PCR amplifications described in the legend to Figure 5 were done with total RNA, not poly A^+ RNA. This confirms that separation of messenger RNA from total RNA on an oligo-dT column was neither necessary to nor important for the PCR amplification conducted by Powell.

50. More significantly, the separation step performed by Powell did not substantially separate the target nucleic acid from other elements of the sample. The "target" nucleic acid in Powell, to the extent it is possible to use that term with reference to Powell, is a particular mRNA associated with a particular gene which is allegedly amplified using PCR. The capture step in Powell captured not only this target mRNA that was subsequently amplified, but also the thousands of other non-target mRNA species present in the cells.

51. Finally, to the extent the claims of the '338 patent are construed as being limited only to non-specific amplification techniques, Powell does not disclose any such non-specific amplification protocol.

52. Neither Chu et al., *Nucleic Acids Research* 14(14):5591-5603 (1986), nor Chu et al, U.S. Patent No. 4,957,858 disclose amplification of target nucleic acids as claimed in the '338 patent. The amplification technique described in Chu is a probe amplification technique where only sequences from the probe and not new sequences from the target are copied. Moreover, to the extent the claims of the '338 patent are construed as being limited only to non-specific amplification techniques, Chu does not disclose any such non-specific amplification protocols.

53. Feix et al., *Proc. Nat'l Acad. Sci. USA* 59(1):145-152 (1968), does not disclose the target capture method that is the subject of the '338 patent. Feix merely refers to a very complicated purification scheme wholly unlike the target capture step of the '338 patent. Further, the purification process cited in Feix does not disclose the use of a capture probe, as claimed in the '338 patent. Moreover, Feix does not refer to purification methods based on hybridization but rather on the basis of size and charge of the nucleic acid molecule via chromatography. Nor does Feix disclose an assay for detection of nucleic acid in a sample. Indeed, to the extent Feix refers to duplication of Qβ RNA sequences, detection of such sequences in clinical samples is totally without any diagnostic

significance. Finally, to the extent the claims of the '338 patent are construed as being limited only to non-specific amplification techniques, Feix does not disclose any such non-specific amplification protocol.

B. Nonobviousness

1. The Claims of the '338 Patent are Nonobvious

54. None of the references identified by Gen-Probe during discovery, either alone or in combination, would have rendered the claims of the '338 patent obvious to a person of ordinary skill in the art as of December 21, 1987.

55. A person of ordinary skill in the art of molecular biology as of December 21, 1987 would have had a Ph.D. in the biological sciences and at least two years of postdoctoral experience. That person would also have developed the skills of using techniques of nucleic acid isolation, characterization, and hybridization, including liquid and solid phase hybridization and the conditions one would use to practice both, cDNA synthesis, gene cloning, affinity chromatography, methods of labeling nucleic acids (both isotopic and non-isotopic methods), DNA sequencing, RNA transcription, and nucleic acid replication and amplification, such as by using DNA or RNA polymerases.

56. As of December 21, 1987, there was no motivation to combine any of the references identified by Gen-Probe pertaining to target capture with any of the references pertaining to amplification in a way that would have resulted in the invention claimed in the '338 patent. To the extent the art provided any motivation at all, it provided a bias against using target capture prior to amplification in nucleic acid detection assays.

57. Indeed, Gen-Probe itself failed to recognize the value of the patented invention prior to December 21, 1987 yet now touts the combination of target capture and amplification as "new" and one of Gen-Probe's five "Core Technologies."

58. Consistent with Gen-Probe's late recognition of the value of target capture before amplification, the early literature taught that nucleic acid amplification based on primers did not require a prior purification step. Accordingly, despite the existence of both nucleic acid

hybridization and amplification techniques prior to the invention, the need for and desirability of nucleic acid target capture and separation prior to *in vitro* amplification in the context of nucleic acid detection assays was not obvious.

59. More specifically, when PCR amplification techniques became available in 1985, there was created a powerful disincentive to employ target capture prior to amplification processes. PCR rapidly became the predominant nucleic acid amplification technique, and PCR was viewed as so specific that it was believed to be unnecessary to purify the target polynucleotide prior to amplification. So strong was the bias in favor of PCR that it essentially removed any motivation for persons of ordinary skill in the art to explore combinations of target capture with amplification, particularly non-specific amplification.

60. It was not until much later that those working in the field of developing nucleic acid detection assays, including Gen-Probe, fully appreciated the need for and desirability of the combination of target capture and separation before *in vitro* amplification.

2. Objective Evidence of Nonobviousness

61. The prior art upon which Gen-Probe relies clearly shows a long-standing failure by those of ordinary skill in the art of designing assays for the detection of nucleic acids in samples to appreciate the invention claimed in the '338 patent. Gen-Probe alleges that methods of specific target capture were known since at least 1977 and that the properties of enzymes needed to amplify target nucleic acids, such as RNA polymerase, were known since the mid 1970s. Yet, nobody combined these technologies in the manner described and claimed in the '338 patent. Even in the early 1990s, several years after the invention of the '338 patent was made, Gen-Probe struggled with problems it encountered in developing assays that used amplification but not target capture. Specifically, the presence of inhibitors in samples was interfering with the amplification step in Gen-Probe's assays, causing a "false negative" result, i.e., the assay failed to detect the target nucleic acid even when it *was* present in the sample. Further, the non-specificity of Gen-Probe's TMA amplification scheme and its predecessors resulted in the amplification of products other than the desired target nucleic acid. Gen-Probe and other companies with amplified assays tried several

different approaches in the early 1990s to overcome these problems, without success. The scientific literature was replete with reports of problems with amplification inhibitors and suggestions for solving the problem *without* target capture throughout the early 1990s.

62. Gen-Probe was not able to solve these problems until it adopted a target capture step prior to amplification in its amplified assays. Incredibly, given Gen-Probe's present contention that a target capture step prior to amplification was "obvious" in 1987, Gen-Probe did not adopt target capture in its FDA-approved assays to overcome these problems until after Vysis' predecessor, Gene-Trak Systems ("Gene-Trak"), suggested to Gen-Probe during a technology exchange between the two companies in 1994 that it should use target capture prior to TMA amplification.

63. Specifically, in April of 1994 Gene-Trak suggested to Gen-Probe that Gene-Trak's target capture technology could fruitfully be combined with Gen-Probe's TMA amplification technology. Some joint experimentation was done to demonstrate the benefits of target capture. The companies disagreed about the results of this testing and the collaboration was discontinued. Almost immediately after the collaboration ended, Gen-Probe researchers, including some who had been involved in the Gene-Trak collaboration, began investigating the use of target capture with Gen-Probe's assays, leading to incorporation of target capture steps into certain Gen-Probe amplified assays. In connection with adding target capture to its assays, Gen-Probe hired Thomas Shimei, William Weisburg, and Jay Shaw from Gene-Trak to work on adding target capture to its assays. Each of these was intimately familiar with Gene-Trak's target capture technology.

64. Gen-Probe found that adding target capture to its amplified assays overcame the problems it had struggled with for years and proceeded to adopt a target capture step in both its HIV/HCV assay and its APTIMA® Combo 2 chlamydia/gonorrhoeae assay. Gen-Probe now promotes target capture combined with amplification as 1) virtually eliminating false negatives caused by sample inhibitors, 2) purifying, not diluting, 3) simplifying sample processing, 4) allowing the use of larger sample volumes, 5) accommodating numerous specimen types, and 6) increasing assay specificity. Gen-Probe has acknowledged that sample processing "has been called the Achilles' heel of first-generation nucleic acid amplification tests" and credits target capture with overcoming the problems of these first generation tests.

65. Another advantage of the invention claimed in the '338 patent is that it facilitates automation of amplified nucleic acid assays. Gen-Probe has touted this advantage as another feature of its HIV/HCV assay and its APTIMA® Combo 2 assay.

66. Gen-Probe recently received FDA clearance to market its APTIMA® Combo 2 assay in the United States. That assay combines target capture with amplification to detect both Chlamydia trachomatis and Neisseria gonorrhoeae bacteria. In its press release, Gen-Probe President and CEO Henry Nordhoff stated "The real significance of this new test is its ability to use urine as a specimen, with the same sensitivity and specificity as the more difficult to obtain endocervical and male urethral swab specimens." It was the addition of target capture to this assay that overcame the amplification inhibition problem in urine samples, enabling the use of urine specimens.

67. If the solution to all these problems, i.e., combining target capture with amplification as disclosed and claimed by the '338 patent, was obvious in 1987, as Gen-Probe now contends, it is difficult to comprehend why Gen-Probe did not use target capture in its FDA-approved amplified assays to overcome the primary problems of amplification inhibition and non-specificity of TMA until after Gene-Trak suggested it to Gen-Probe in 1994. The answer is that the benefits of combining target capture with amplification were *not* obvious to Gen-Probe and would not have been obvious to those skilled in the art in 1987. Gen-Probe's failure to adopt target capture to overcome the problems prevalent in its amplified assays until after Gene-Trak told Gen-Probe to do so shows that the concept of combining target capture with amplification was not obvious.

68. In addition, the evidence demonstrates commercial success or expected commercial success of products produced in accordance with the '338 patent claims. Gen-Probe has stipulated that it expects its HIV/HCV assays to be commercially successful. Chiron projects annual sales of over $500 million for the HIV/HCV assay. In addition, the fact that Gen-Probe, bioMerieux Vitek, Inc., Chiron, and Bayer took licenses under the '338 patent is further evidence of commercial success and nonobviousness.

C. Enablement

1. The Specification Enables Non-specific Amplification by Using Random Primers

69. The specification enables practice of the invention in a variety of ways, including those illustrated in Examples 4-7. With specific reference to Example 5 of the '338 patent, it discloses methods of amplifying a target nucleic acid. One of the methods disclosed in Example 5 employs random primers in conjunction with a DNA polymerase to form double stranded DNA from a target nucleic acid. The example then discloses the use of RNA polymerase lacking sigma subunit to produce many RNA copies of that DNA. Persons of ordinary skill in the art would have been able to practice the patented invention without undue experimentation using techniques similar to that discussed in Example 5 as of December 21, 1987.

70. Example 6 of the '338 patent describes use of the Klenow fragment of DNA polymerase in appropriate buffer with random oligonucleotide primers to bring about non-specific double-stranded DNA synthesis. Example 6 describes successive rounds of DNA denaturation, reagent addition, and polymerization to further amplify the DNA. Persons of ordinary skill in the art would have been able to practice the patented invention without undue experimentation using techniques similar to that discussed in Example 6 as of December 21, 1987.

71. The use of random primers for the generation of DNA product, including denaturation conditions, annealing conditions, polymerization conditions, and quantification, is described in Feinberg and Vogelstein, *Analytical Biochemistry* 132:6-13 (1983). It is clear from the description in that publication that there is enormous latitude in the reaction conditions that would permit successful DNA synthesis. These techniques were well known to persons of ordinary skill in the art in December of 1987.

72. While Feinberg and Vogelstein did not use repeated cycles of thermal denaturation and renaturation to amplify the target nucleic acid, such an approach is disclosed in Example 6 of the '338 patent and also is clearly described in U.S. Patent No. 4,683,202 (July 28, 1987) ("the '202 patent"), which describes the widely known PCR procedure. The '202 patent describes a variety of

reaction conditions that would permit successful amplification of a target nucleic acid using thermal cycling.

73. While the '202 patent describes conditions for amplification using specific primers, the non-specific primers described in Example 6 of the '338 patent could have been used in a manner analogous to the use of specific primers in the '202 patent without undue experimentation.

74. The optimization of any *in vitro* nucleic acid amplification scheme in December of 1987, even PCR, often required a substantial amount of experimentation. Such experimentation was not undue. Moreover, it was well understood by those skilled in the art that reaction conditions (such as concentration of primers, polymerases, and dNTPs, incubation times and temperatures, pH, and buffer components) could be varied while still achieving amplification of a target nucleic acid. Varying those conditions was considered to be routine by those skilled in the art. Thus, one skilled in the art could have performed the procedures described in the '338 patent of amplification by using random primers without undue experimentation as of December 21, 1987.

75. Gene-Trak's decision not to commercially pursue an amplification scheme involving random primers has no bearing on the enablement of the claims of the '338 patent. Gene-Trak intended to pursue a probe amplification technology based on Qβ replicase in developing its commercial assays. Although a novice Gene-Trak scientist without a Ph.D. degree undertook a handful of preliminary amplification experiments using random primers for purposes of comparison to the Qβ system, little time and resources were devoted to that endeavor. Nevertheless, by the time such experiments were terminated, amplification of the target had been shown.

2. The Specification Enables Amplification by the Alternative Disclosure of Example 5 Using the Specific Capture Probe as the Primer

76. The specification of the '338 patent also discloses a method of amplifying the target polynucleotide by using the specific capture probe as the primer. This method, disclosed in Example 5, is more specific than the method of using random primers for amplification. The only double stranded DNA present in the system after second strand synthesis primed by the capture probe will be the target polynucleotide. While core RNA polymerase used to copy that DNA into RNA is not a "specific" enzyme, the only double stranded DNA available for copying will be the target DNA.

Moreover, a thermal cycling reaction of the sort described in Example 6 using the capture probe as primer according to Example 5 would also result in more specific amplification of the target. Persons of ordinary skill in the art would have been able to practice the patented invention using the specific capture probe as a primer without undue experimentation as of December 21, 1987.

3. The Specification Enables Practice of the Invention Using PCR

77. The specification of the '338 patent is generic as to the specificity or non-specificity of the target amplification techniques that can be used in the claimed methods. The specification certainly contemplates the use of specific primers to amplify the target polynucleotide. Though the specification states that the use of specific primers is unnecessary, it does not say that one could not or should not use them. Moreover, PCR was the most famous amplification method known at the time of filing of the application that led to the issuance of the '338 patent. The practice of PCR was enabled by publications of Dr. Kary Mullis and his colleagues before December 21, 1987. The PCR process can be practiced in ways that result in substantial non-specific amplification, which would enable practice of the claimed invention, even as narrowly construed by the Court, without undue experimentation as of December 21, 1987.

4. The Specification Enables Non-specific Amplification by Using Qβ Replicase

78. The specification of the '338 patent suggests that Qβ replicase could be used in a similar manner to generate amplification products from target polynucleotide templates. This is described in Example 7 of the specification. Example 7 describes the amplification process by first purifying an rRNA or RNA transcribed from target DNA with a capture probe, denaturing the hybrid duplex and replicating the target RNA using Qβ replicase to form a double-stranded molecule. These procedures are described elsewhere in the specification or were well known in December 1987. Upon completion of the initial replication, thermal cycling and addition of fresh Qβ replicase could be used to further amplify the target RNA.

79. For example, the purification of target nucleic acids from the sample using a capture probe is described in great detail in the specification and examples. Denaturing techniques, such as

by heating, to separate the hybrids were well known. Non-specific replication of single stranded target RNA using QB replicase was also well known. For example, Blumenthal, Proc. Natl. Acad. Sci. U.S.A. 77:2601-2604 (1980) and references cited therein teach the replication of any template molecule. Further, Methods in Enzymology (1979) 60:628, cited in Example 7, teaches the purification of Qβ replicase.

80. QB replicase is normally highly specific with respect to the template molecules it will replicate. However, it was known that this high specificity could be relaxed to allow more general replication by the enzyme. This also increased amplification efficiency by increasing enzyme replication efficiency. For example, Blumenthal, Proc. Natl. Acad. Sci. U.S.A. 77:2601, (1980), cited in Example 7, and references cited therein (e.g., Blumenthal and Carmichael, Ann. Rev. Biochem 48:525-48 (1979), and Feix, "Primer Directed Initiation of RNA Synthesis Catalysed by QB Replicase," Biochemical and Biophysical Research Communications, Vol. 65(2):503-509 (1975)) discuss various reaction conditions by which the normal template specificity of Qβ replicase can be relaxed. These include increasing the Mn^{2+} concentration of the reaction system, increasing dGTP concentration, lowering ionic strength, adding glycerol, adding oligo C to the 3' end of the template, and use of oligonucleotide primers. Gen-Probe has not proven that this technique is inoperative.

IV. Unenforceability

81. Gen-Probe has alleged that Vysis committed inequitable conduct during the prosecution of the patent applications that led to the issuance of the '338 patent. Vysis vigorously disputes those allegations.

82. None of the information alleged by Gen-Probe to have been withheld or misstated during the prosecution of the '338 patent was material to the patentability of the inventions claimed in the '338 patent.

83. Gen-Probe has not proven and cannot prove that anyone connected with the prosecution of any of the applications that led to the issuance of the '338 patent had any intent to deceive the PTO.

84. There was nothing improper about the request for Certificate of Correction in this case, or in its grant, or in the associated amendments to the abandoned applications.

85. U.S. Patent Application Serial Number 07/944,505 ("the '505 application") became abandoned unintentionally. The attorney prosecuting that application, Norval Galloway had no intention to abandon the application, had no authority to allow an application to go abandoned, and continued to prosecute counterpart foreign applications. At the time he was prosecuting the '505 application, Mr. Galloway carried a heavy workload that included litigation responsibilities. Moreover, the prior abandonment of the '505 application is wholly irrelevant to Vysis' subsequent correction of the claim of priority of the '338 patent.

86. Gen-Probe has alleged that certain documents cited by the European Patent Office during the prosecution of a European counterpart to the '338 patent office should have been disclosed to the PTO.

87. Document EP-A-0265244 is the European counterpart of Dr. Collins's U.S. Patent Application Serial No. 922,155, which is the parent application of (and is incorporated by reference in) each of the applications in the chain of applications that ultimately issued as the '338 patent. Document EP-A-0265244 is not prior art to the '338 patent, as it was published after December 21, 1987.

88. Document EP-A-0200362 is the European counterpart of Dr. Kary Mullis's United States patent applications concerning PCR. That document is identical in all substantive aspects to the Mullis '195 patent considered by the Examiner during prosecution of the applications that ultimately issued as the '338 patent.

89. The European Patent Office identified documents EP-A-0154505, WO-A-8605815, and WO-A-8701730 as providing "technological background." Those documents provide merely background information. The information disclosed in those documents is less relevant than the prior art that was considered by the Examiner during prosecution in the PTO of the applications that ultimately issued as the '338 patent.

90. Gen-Probe has alleged that the applicants for the '338 patent should have disclosed to the Patent Office an informal conversation that Dr. Lawrie had with Tom Gingeras during a

conference. There was no duty to disclose that conversation because it does not constitute prior art to the '338 patent.

91. Gen-Probe has alleged that failure to disclose the Chu '858 patent to the Patent Office during prosecution of the '338 patent violates the applicant's duty of disclosure. The Chu '858 patent discloses a probe amplification technology different from the target amplification technique claimed in the '338 patent and is, therefore, immaterial. Chu does not disclose sequence-specific target capture and is immaterial for this reason as well. Moreover, there is no evidence that anyone subject to the duty of disclosure under 37 C.F.R. § 1.56 recognized the disclosure in the Chu patent as material to the patentability of the '338 patent during prosecution of the '338 patent.

92. Gen-Probe further contends that the applicants violated their duty of candor by failure to disclose that Examples 6 and 7 of the '338 patent are inoperative. First, Gen-Probe has not established that these Examples are inoperative. Second, there is no evidence that the inventors knew or believed that Examples 6 and 7 were inoperative.

93. Gen-Probe also contends that failure to disclose the Lizardi et al. pre-publication manuscript misled the Examiner. That document, however, is not prior art to the '338 patent and thus there was no duty to cite it.

94. Gen-Probe has also alleged that the '338 patent should be unenforceable on the grounds of laches during the prosecution of the patent. Vysis vigorously disputes this allegation. No intentional, unreasonable, or inexcusable delay of prosecution of the '338 patent ever occurred. Further, Gen-Probe has not provided any evidence of prejudice as a result of the prosecution of the '338 patent. Moreover, the courts do not recognize "prosecution laches" as a viable defense.

V. Unfair Competition

95. No facts that establish the invalidity and/or unenforceability of the claims of the '338 patent exist. Vysis has not acted unfairly, inequitably, or in bad faith with respect to the claims of the '338 patent or the '338 license agreement.

96. The '338 patent is presumed valid under the patent statute. Vysis did not insist that Gen-Probe take a license under the '338 patent. Rather, Gen-Probe insisted that it be granted a

license. Vysis has not sued Gen-Probe for infringement of the '338 patent, and Vysis' defense of Gen-Probe's allegations in this case is protected conduct under the United States Constitution and the laws of the state of California.

POINTS OF LAW

I. Infringement

97. Vysis has not contended that Gen-Probe infringes the '338 patent, as Gen-Probe is licensed under that patent and has not repudiated the license. Nevertheless, Vysis does contend that but for the license agreement, Gen-Probe's HIV/HCV assay would infringe the claims of the '338 patent.

98. Determining infringement is a two-step process: the Court first construes the claims of the patent, and then the fact finder applies the properly construed claims to the accused device. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

99. The second part of the test for finding infringement requires a determination as to whether the accused device contains each limitation of the asserted claim, either literally or by equivalents. *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1580 (Fed. Cir. 1989).

100. Literal infringement is shown if the accused device contains each and every limitation of the claim as properly construed. *Amhil Enters., Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1562 (Fed. Cir. 1996).

101. Even if the accused device does not literally infringe the claim, it can still infringe under the doctrine of equivalents. Under the doctrine of equivalents, "insubstantial differences" between a claim limitation and the corresponding element or elements in the accused device will not avoid infringement. The inquiry is simply whether the accused device contains elements that are equivalent to those claimed in the patent. A useful test for equivalence is whether the claimed and substituted element perform substantially the same function, in substantially the same way, to attain substantially the same results. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39-40 (1997).

102. Under the doctrine of equivalents, comparing a claim to the accused device is made on an element-by-element basis, but the comparison must be made in the context of the claimed invention. *Id.*; *Canton Bio-Medical, Inc. v. Integrated Liner Techs., Inc.*, 216 F.3d 1367, 1370 (Fed. Cir. 2000).

103. The issuance of a patent to an alleged infringer does not raise any presumption that the alleged infringer's product or method avoids infringement, either literally or by equivalence. *See Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1580-81 (Fed. Cir. 1984). As long as the accused method includes all of the elements of the patent claim, or if the method is found to be equivalent under the doctrine of equivalents, then that claim is infringed by the accused method notwithstanding the existence of a patent on that accused method. *Id.*

II. Validity

104. A patent is presumed valid. 35 U.S.C. § 282. Each claim of a patent is presumed valid independently of the other claims. *Id.*; *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992). Thus, the patent is presumed to be novel and not anticipated (under 35 U.S.C. § 102), to be non-obvious (under 35 U.S.C. § 103), and to be fully described and enabled by the written disclosure (under 35 U.S.C. § 112, ¶ 1). *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed. Cir. 1986) (patent is presumed to be novel and non-obvious); *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) (patent is presumed to satisfy § 112).

105. Given this strong presumption of validity, Gen-Probe has the burden of proving invalidity by clear and convincing evidence. *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984).

A. The Effective Filing Date of the Claims of '338 Patent

106. Each claim of the '338 patent is entitled to an effective filing date of December 21, 1987, because the claims satisfy each requirement of 35 U.S.C. § 120 with respect to U.S. Patent Application Serial Number 07/136,920, from which the '338 patent claims priority.

B. Novelty

107. The standard for proving lack of novelty or anticipation under 35 U.S.C. § 102 is one of strict identity. To prove anticipation of a claim of the '338 patent, Gen-Probe must show, by clear

and convincing evidence, that a single prior art reference (1) contains each and every element of the claim, and (2) enables one of ordinary skill to make and use the anticipating subject matter. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996); *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991); *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990). If even one element is not shown in the reference, then it does not anticipate. Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984). Moreover, the single source must disclose all of the claimed elements "arranged as in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).

108. The classic test for anticipation is whether the prior art reference would literally infringe if it came later: "That which infringes, if later, would anticipate, if earlier." *Knapp v. Morss*, 150 U.S. 221, 228 (1893); *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1459 (Fed. Cir. 1984).

C. Nonobviousness

109. Obviousness is a conclusion of law based on the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Under the standard of *Graham*, an analysis of obviousness requires consideration of (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed subject matter as a whole, (3) the level of skill in the art, and (4) objective evidence of nonobviousness. The claimed invention must be viewed in the state of the art that existed at the time of invention, and it is improper to use hindsight to reconstruct the claimed invention from the prior art. *ACS Hospital Sys. Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir. 1988).

110. In ascertaining the scope and content of the prior art, it must be determined whether the publication or patent relied upon by the challenger is in the prior art under 35 U.S.C. § 102. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987). To evaluate the

obviousness of claimed subject matter, the particular reference relied upon must constitute "analogous art." *In re Clay*, 966 F.2d 656, 658-59 (Fed. Cir. 1992).

111. After having ascertained the scope and content of the prior art, the claims must be compared to the prior art. *Panduit*, 810 F.2d at 1566-68. "It is impermissible . . . to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965).

112. Prior art references may not be combined unless those references teach or suggest the particular combination to one of ordinary skill in the relevant art. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 293 (Fed. Cir. 1985). What a reference teaches and whether it suggests a particular combination is a question of fact addressed to one of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). Where the prior art "teaches away" from the claimed invention rather than motivating a person of ordinary skill in the art to do what the patentee has done, the claimed invention is nonobvious. *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983). The prior art must motivate a person skilled in the art to do what the patentee has done. *See In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995). It must also provide a reasonable expectation of success. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

113. The assessment of obviousness requires examination of certain objective evidence of nonobviousness: the extent of commercial success of the patented invention, whether the invention satisfies long-felt needs, whether others have failed to find a solution to the problem plaguing the art, any copying of the invention by others, and the extent of industry acquiescence in the invention's merit through licensing it. *Id.*; *see also Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998); *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Dow Chem. Co. v. American Cyanamid Co.*, 816 F.2d 617, 622 (Fed. Cir. 1987); *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983). A court must always consider such objective evidence in determining the obviousness of the claimed invention. *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d

1568, 1573 (Fed. Cir. 1996) (error of law for district court to ignore objective evidence); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

D. Enablement

114. The burden is on the party challenging validity to prove by clear and convincing evidence that the claims of a patent are invalid for lack of enablement. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1359 (Fed. Cir. 1998).

115. Patents are written for those of ordinary skill in the art. Thus, the enablement requirement of 35 U.S.C. § 112, ¶ 1, is met if one of ordinary skill in the art could make and use the invention without undue experimentation. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). Moreover, "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." *Id.* Accordingly, the specification need not expressly teach what is already known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384 ("a patent need not teach, and preferably omits, what is well known in the art"). Inferences based on the skill in the art are thus permissible and can demonstrate enablement. "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998).

116. A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed. *Johns Hopkins*, 152 F.3d at 1360. Moreover, the party challenging enablement must demonstrate that those attempting to make and use the claimed invention are of ordinary skill in the art. *Id.*

117. In the biological sciences, a substantial amount of routine experimentation is often required to practice an invention, and this is not undue experimentation. *See, e.g., In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of

how to practice a desired embodiment of the invention claimed." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quotation and citation omitted).

118. Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971); *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. *In re Chilowsky*, 229 F.2d 457, 461 (C.C.P.A. 1956); *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

119. That some embodiments within the scope of a patent claim may not work is not fatal to enablement as long as the number of such embodiments is not so large that undue experimentation would be required to determine which embodiments work and which do not. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). Enablement does not require disclosure of a commercializable invention. *See Christianson v. Colt Indus. Operating Corp.*, 822 F.2d 1544, 1562 (Fed. Cir. 1987), *vacated on other grounds*, 486 U.S. 800 (1988).

120. Experimentation that is otherwise reasonable is not rendered unreasonable merely because there is a technical or factual error in the examples of the specification, provided one of ordinary skill in the art could easily detect the error. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)

III. Unenforceability

A. Inequitable Conduct

121. Inequitable conduct is an equitable defense to be decided by the Court even in a jury trial. *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1318 (Fed. Cir. 2000).

122. "Inequitable conduct includes affirmative misrepresentations of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998) (citations omitted). Inequitable conduct entails a two-step analysis: first, a determination of whether the withheld information meets a threshold level of materiality and intent to mislead, and second, a

weighing of the materiality and intent "[i]n light of all the circumstances" to determine "whether the applicant's conduct is so culpable that the patent should be held unenforceable." *Id.* Both intent and materiality are questions of fact. *Id.*

123. Proof of inequitable conduct requires proof of an actual intent to deceive, not merely mistake, negligence, or even gross negligence. *Kingsdown Medical Consultants, Ltd. v. Hollister, Inc.*, 63 F.2d 867, 876 (Fed. Cir. 1988) (en banc).

124. Information is not material if it is cumulative to information already before the PTO or if it would not provide a basis for rejecting the claims. 37 C.F.R. § 1.56 (1992). Information lacking specificity and disclosure to support a rejection under 35 U.S.C. § 102(g) also is not material. *Life Techs., Inc. v. Clonetech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

125. Inequitable conduct must be proven by clear and convincing evidence. *See Seiko Epson Corp. v. Nu-Kote International, Inc.*, 190 F.3d 1360, 1367 (Fed. Cir. 1999) ("A ruling of inequitable conduct in the PTO must be supported by clear and convincing evidence of material misrepresentation, made with the intent to deceive or mislead the patent examiner.")

126. Recognizing the heavy burden of proof to establish a defense of inequitable conduct, the Federal Circuit has disapproved of the frequency with which the defense is raised. "[T]he habit of charging inequitable conduct in almost every major patent case has become an absolute plague." *Burlington Indus., Inc. v. Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988). *Accord Ortho Pharmaceutical Corp. v. Smith,* 18 U.S.P.Q.2d 1977, 1991 (E.D. Pa. 1990), *aff'd*, 959 F.2d 936 (Fed. Cir. 1992) ("Inequitable conduct is a much-abused and too often last-resort allegation. . . . As in many patent cases, the issue of inequitable conduct deflects the court's attention from the issues of validity and infringement. . . . [A challenger] in complex litigation should not be permitted to sidestep these main issues by nit-picking the patent file in every minute respect with the effect of trying the patentee personally, rather than the patent.").

B. "Prosecution Laches"

127. Courts that have considered the defense of "prosecution laches" have declined to recognize it as a viable defense. For example, the Northern District of California in *Advanced*

Cardiovascular Systems, Inc. v. Medtronic, Inc., 41 U.S.P.Q.2d 1770 (N.D. Cal. 1996), granted a motion to strike an affirmative defense of prosecution laches:

> Since the only delay that can form the basis of a laches defense is delay between the issuance of the patent and the filing of the infringement action, defendant's theory of laches based on delay in prosecution of the patent is not cognizable.
>
> Furthermore, since there is no allegation that plaintiff violated any of the statutory or regulatory rules for prosecuting patents, there was no improper delay in the prosecution of this patent to justify a laches or equitable estoppel defense. The '346 patent issued from a series of "continuation" applications relating back to the original application filed on January 6, 1987. Under 35 U.S.C. § 120, the prosecution of this patent dates back to the filing of the original application. *Transco Prods., Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 556 (Fed. Cir. 1994). By providing this relation back doctrine, Congress evidenced a clear intent to regulate the timing of continuation applications. Accordingly, only Congress can determine what constitutes unreasonable delay in the filing of such an application. It is not for this Court to decide that the prosecution of a patent according to the rules of the PTO is unreasonable and inequitable. Since defendant's laches and equitable estoppel defenses ask the Court to make precisely this determination, the Court strikes these defenses with prejudice.

Id. at 1774-75.

128. Still other courts that have considered prosecution laches have declined to recognize it as a defense. *See, e.g., Haney v. Timesavers, Inc.*, 900 F. Supp. 1378, 1382 (D. Or. 1995); *Ford Motor Co. v. Lemelson*, 42 U.S.P.Q.2d 1706 (D. Nev. 1997); *Progressive Games, Inc. v. Amusements Extra, Inc.*, 83 F. Supp.2d 1180, 1183-85 (D. Colo. 1999).

IV. Unfair Competition

129. The '338 patent license agreement provides that royalties shall be paid unless and until a licensed patent claim is declared invalid in a final decision from a tribunal of competent jurisdiction from which no appeal has or can be taken. This is in accord with the substantive patent law, which provides that (a) a patent is presumed valid (35 U.S.C. § 282); (b) the party asserting invalidity has the burden of proving that the patent is invalid by clear and convincing evidence (*Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1423 (Fed. Cir. 1988)); and (c) a licensee wishing to retain the benefits of a patent license must continue to pay royalties until the presumptively valid patent is declared invalid (*Cordis Corp. v. Medtronic, Inc.*, 780 F.2d 991, 994-95 (Fed. Cir. 1985)).

130. Thus, Vysis' alleged persistence in its belief that the patent remains valid and enforceable and that Gen-Probe is obligated to make royalty payments in accordance with the terms of the license is simply declaratory of Gen-Probe's obligations under a valid contract. California Business & Professions Code § 17200 cannot convert activity authorized by law into a tort. *Cel-Tech Communications, Inc. v. Los Angeles Cellular Tel. Co.*, 20 Cal.4th 163, 182 (1999)

131. If Gen-Probe is implying that Vysis' decision to defend itself in this lawsuit is the act of "enforcement" constituting unfair competition the allegation of violation of California Business & Professions Code § 17200 must fail because this action is specifically authorized under the litigation privilege of California Civil Code §47(b) and cannot, therefore, constitute unfair competition. *Cel-Tech*, 20 Cal.4th at 182-83 (*referring to Rubin v. Green*, 4 Cal.4th 1187 (1993)); *see also California Physicians' Service v. Superior Court*, 9 Cal.App.4th 1321, 1325 (1992) ("[t]here is no tort of 'malicious defense.' The mainstay supporting this principle is the absolute privilege contained in Civil Code section 47, subdivision (b).") (citation and footnote omitted).

ABANDONED ISSUES

132. Gen-Probe has not identified any evidence during discovery to support its claims of "prosecution laches" and unfair competition. Accordingly, Vysis believes those issues have been abandoned.

133. Gen-Probe has also failed to identify any evidence or submit any expert reports concerning its allegations of abandonment under 35 U.S.C. § 102(c) and anticipation under 35 U.S.C. § 102(f). Accordingly, Vysis believes that Gen-Probe has abandoned those theories of anticipation.

134. Gen-Probe has failed to submit any expert reports concerning its contentions that the '338 patent is anticipated by a Wang et al. publication it has identified or by Boss, *J. Biol. Chem.* 256:12958-12961 (1981). Accordingly, Vysis believes that Gen-Probe has abandoned those theories of anticipation.

135. Gen-Probe has failed to submit any expert reports concerning its contentions that the '338 patent is obvious in view of Strair, *PNAS* 74:4346-4360 (1977), Hirsch, *PNAS* 75:1736-1739 (1978), Montgomery, *J. Biol. Chem.* 257:7756-7761 (1982), Boss, *J. Biol. Chem.* 256:12958-12961 (1981), or Georgiev, *Science* 195:394-397 (1977). Accordingly, Vysis believes that Gen-Probe has abandoned those theories of obviousness.

136. Vysis believes that Gen-Probe has abandoned its theory of inequitable conduct based on the alleged misleading arguments about the Mullis reference, as pled in ¶¶ 76-78 of Gen-Probe's 2nd Amended Complaint.

EXHIBITS

Prediction of which exhibits Vysis will offer into evidence is difficult at this time because Gen-Probe bears the burden of proof on virtually every issue in this case. The materials Vysis will actually present will depend in large measure on the materials Gen-Probe chooses to present, which cannot yet be predicted with certainty. A list of the exhibits Vysis currently expects it may offer in evidence is attached as Exhibit A.

WITNESSES

Fact Witnesses

Prediction of which witnesses Vysis will actually call is currently subject to the same uncertainty affecting identification of Exhibits. The fact witnesses that Vysis currently expects it may call, either live or by deposition, are:

NAME	ADDRESS
Becker, Michael	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Bishop, John	Vysis, Inc. 3100 Woodcreek Drive Downers Grove, IL 60515 Tel: 630-271-7000
Brentano, Steve	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Galloway, Norval	Vysis, Inc. 3100 Woodcreek Drive Downers Grove, IL 60515 Tel: 630-271-7000
Harpold, Michael	5920 North Placita Tecolote Tucson, Arizona 85718
Harvey, Richard	Dako Corporation 6392 Via Real Carpenteria, CA 93013
Hill, Craig	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001

Kacian, Daniel	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
King, Walter	Vysis, Inc. 3100 Woodcreek Drive Downers Grove, IL 60515 Tel: 630-271-7000
Lane, David	Hamilton Thorne Biosciences, Inc. 100 Cummings Center, Suite 102C Beverly, MA 01915 Tel: 978-921-2050
Longiaru, Matthew	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Majlessi, Mehrdad	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
McDonough, Sherrol	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Mimms, Larry	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Mullis, Kary	919 Bayside Drive Apartment O-4 Newport Beach, CA 92660
Nelson, Norman	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Shaw, Jay	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Shimei, Thomas	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001
Weisburg, William	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121 Tel: 800-523-5001

If needed to establish the admissibility of documents, Vysis may call a custodian of documents from either Gen-Probe or Vysis.

Expert Witnesses

Vysis expects to call the following expert witnesses:

NAME	ADDRESS
Andrew P. Feinberg, Ph.D., M.P.H.	Johns Hopkins University School of Medicine Ross Building, Room 1064 720 Rutland Avenue Baltimore, Maryland 21205 Tel.: 410-614-3489

Qualifications and Testimony:

Dr. Feinberg received his bachelors degree, M.D., and M.P.H. degrees from Johns Hopkins University in 1973, 1976, and 1981, respectively. He performed research fellowships at the University of California San Diego from 1977 to 1979 and at Johns Hopkins University School of Medicine from 1981 to 1983. During the latter period he invented the random priming procedure for labeling DNA. This work was published in *Analytical Biochemistry*, vol. 132, pp. 6-13 (1983), "A Technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity," by Andrew P. Feinberg and Bert Vogelstein. In addition, he wrote a review article on this subject in 1991, Andrew P. Feinberg, "Labeling of Probes by the Random Primer Procedure," published in *Methods in Gene Technology*, vol. 1, pp. 63-70.

His awards include general honors of Johns Hopkins University; Phi Beta Kappa; Delta Omega; Johns Hopkins University School of Medicine award for postdoctoral investigation; Fellow of the American College of Physicians; Member, American Society for Clinical Investigation; Member, Association of American Physicians; Institute for Scientific Information most-cited authors list; and Dean's Lecturer at Johns Hopkins University School of Medicine and the University of Kentucky School of Medicine. He was an instructor in Medicine from 1979 to 1980, and Assistant Professor of Oncology and Medicine from 1983 to 1986, at Johns Hopkins University School of Medicine. He was an Assistant and Associate Professor of Internal Medicine and Human Genetics

at the University of Michigan from 1986 to 1994 as well as a Howard Hughes Investigator at that institution. Since 1994, he has been King Fahd Professor of Molecular Medicine in the Institute of Genetic Medicine and the Department of Medicine at Johns Hopkins University School of Medicine, with joint appointments in Oncology and Molecular Biology & Genetics. He is the author of over 100 articles, including 78 peer-reviewed original reports.

Dr. Feinberg will provide testimony concerning the enabling disclosure of the '338 patent with respect to non-specific amplification of a target nucleic acid. The details and scope of Dr. Feinberg's expected testimony are more fully disclosed in paragraphs 69-75 above, in his expert report, and in the testimony given at his deposition, which are incorporated by reference into this Memorandum. Dr. Feinberg may also rebut evidence provided at trial by Gen-Probe.

NAME	ADDRESS
David H. Persing, M.D., Ph.D.	Corixa Corporation Seattle Life Sciences Center, Suite 200 1124 Columbia Street Seattle, Washington 98104 Tel.: 206-754-5711

Qualifications and Testimony:

Dr. Persing is an expert in the field of molecular biology. He is presently Vice President, Molecular Biology, at Corixa Corporation, and Medical Director, Infectious Disease Research Institute, both in Seattle, Washington. He received a Ph.D. (Department of Biochemistry and Biophysics) and an M.D. (School of Medicine) from the University of California, San Francisco in 1988. His Ph.D. work was performed in the laboratory of Nobel laureate Harold Varmus. He was a Resident and Research Fellow at the Yale School of Medicine from 1988 to 1990. He was employed by the Mayo Clinic, Rochester, Minnesota from 1990 to 1999.

Dr. Persing's work has been primarily directed to the study of infectious diseases, including the study of the application of nucleic acid hybridization assays in medical diagnostics. From 1993 to 1999, he was director of the Molecular Microbiology Lab of the Mayo Clinic, which was one of

the premier centers for the diagnosis of infectious diseases by molecular methods. There, he pioneered techniques for pathogen discovery and contamination control, and discovered several new pathogens.

Dr. Persing will provide testimony concerning the equivalence between the TMA amplification process used in Gen-Probe's HIV/HCV assays and the amplification techniques disclosed and claimed in the '338 patent. Dr. Persing will also testify concerning the novelty and nonobviousness of the inventions claimed in the '338 patent. The details and scope of Dr. Persing's expected testimony are more fully disclosed in paragraphs 14-77 above, in his expert report, and in the testimony given at his deposition, which are incorporated by reference into this Memorandum. Dr. Persing may also rebut evidence provided at trial by Gen-Probe.

NAME	ADDRESS
John Witherspoon	815 Connecticut Avenue, N.W. Washington, D.C. 20006 Tel.: 202-835-3700

Qualifications and Testimony:

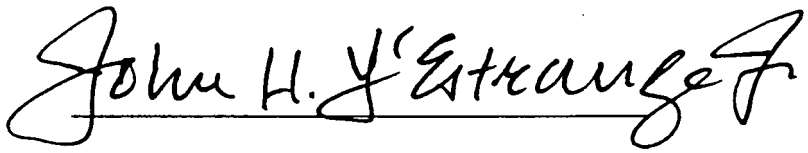
Mr. Witherspoon is an attorney specializing in patent law. Since 1992, he has also been Distinguished Professor of Intellectual Property Law and Coordinator of the specialty track in Intellectual Property Law at the George Mason University School of Law in Arlington, Virginia. From 1998-2000, he served as an Adjunct Professor of Law at the Georgetown University Law Center in Washington, D.C. He has been in the private practice of patent law for over twenty-seven years. In addition, he served as an Examiner-in-Chief and member of the Board of Appeals of the PTO from 1971-1978; and as Law Clerk and Technical Adviser to Judge Giles Sutherland Rich at the United States Court of Customs and Patent Appeals, a predecessor court to the United States Court of Appeals for the Federal Circuit from 1964-1966. Mr. Witherspoon has been found qualified to give expert testimony concerning United States patent practices and procedures at 66 trials in patent cases before United States district courts throughout the country, including this Court,

and at six hearings involving patent matters before the United States International Trade Commission.

Mr. Witherspoon will provide testimony concerning practices and procedures before the PTO. Mr. Witherspoon will also provide testimony concerning the absence of inequitable conduct in connection with the prosecution of the patent applications that led to the issuance of the '338 patent, as well as the post-issuance amendments and Certificate of Correction. He will also provide testimony, if needed, regarding the effective filing date of the '338 patent. The details and scope of Mr. Witherspoon's expected testimony are more fully disclosed in paragraphs 81-94 above, in his expert report, and in the testimony given at his deposition, which are incorporated by reference into this Memorandum Mr. Witherspoon may also rebut evidence provided at trial by Gen-Probe.

Date: January 14, 2002

WRIGHT & L'ESTRANGE



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Attorneys for Defendant Vysis, Inc.

CERTIFICATE OF SERVICE

I, the undersigned, declare under penalty of perjury that I am over the age of eighteen years and not a party to this action; my business address is 4665 Park Blvd., San Diego, California 92116; and that I served the below-named persons the following documents:

DEFENDANT VYSIS' MEMORANDUM OF CONTENTIONS OF FACT AND LAW

in the following manner:

1. ___X___ By personally delivering copies to the person served.

2. _____ By leaving, during usual office hours, copies in the office of the person served with the person who apparently was in charge and thereafter mailing (by first-class mail, postage prepaid) copies to the person served at the place where the copies were left.

3. _____ By leaving copies at the dwelling house, usual place of abode, or usual place of business of the person served in the presence of a competent member of the household or a person apparently in charge of his office or place of business, at least 18 years of age, who was informed of the general nature of the papers, and thereafter mailing (by first-class mail, postage prepaid) copies to the person served at the place where the copies were left.

4. _____ By placing a copy in a separate envelope, with postage fully prepaid, for each address named below and depositing each in the U.S. Mail at San Diego California on January 14, 2002.

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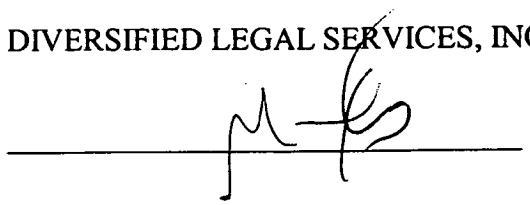
Executed on January 14, 2002, at San Diego, California.

DIVERSIFIED LEGAL SERVICES, INC.



EXPERT REPORT OF MARK S. BERNINGER PURSUANT TO FED.R.CIV.P. 26

I have been retained as an expert witness in this action by Gen-Probe Incorporated and have agreed to testify at the trial of this action on the issue of whether the disclosures of U.S. Patent No. 5,750,338 ("the '338 patent") would have enabled one of ordinary skill in the art to achieve significant or exponential amplification using random primer amplification as of the filing date of the application for the patent.

SUMMARY OF MY OPINION

I have considered the disclosures of the '338 patent, particularly with regard to the teachings of Example 6. Having reviewed the specification of the '338 patent, I conclude that the patent's disclosures completely failed to enable one of ordinary skill in the art to achieve exponential amplification using random primers and the Klenow fragment of *E. coli* DNA polymerase (hereinafter referred to as "Klenow polymerase").

EDUCATION AND EXPERIENCE

My relevant training and experience are briefly summarized here. I received a A.B. in Biology from Columbia University in 1970. During the period 1970-1978 I undertook post-graduate work in Biology and was employed as a research assistant and instructor at Massachusetts Institute of Technology. I was employed by Life Technologies, Inc. in the following positions for seventeen years (from 1978 through 1995): New Product Development Manager; Research Director, Molecular Virology; Research Director, Molecular Probe Technology; and Director, Intellectual Property and Technology Acquisition. While employed by Life Technologies in 1986, I also became a registered U.S. Patent Agent with the United States Patent and Trademark Office. From 1995 to 1997, I was employed by Gen-Probe Incorporated as Vice President, Business Development. At present, I am employed as Vice President, Business Development by the American Type Culture Collection, Manassas, Virginia. A true and correct copy of my *Curriculum Vitae* is attached to this declaration as Exhibit "A."

I am familiar with efforts to use random primers to amplify DNA because of my own extensive research in this area. Beginning in 1988, while I was employed by Life Technologies, Inc., I worked closely with Dr. James Hartley in initial work on random primer amplification methods developed at Life Technologies, Inc. Dr. Hartley invented a method of random primer amplification ("RPA") as claimed in U.S. Patent No. 5,043,272. I was co-inventor with Dr. Hartley on U.S. Patent No. 5,106,727, which claims an improvement invention related to the RPA method disclosed in the '272 patent.

I have stayed abreast of the general technology of amplification by regularly reviewing scientific literature and attending scientific conferences. My conclusions as provided below are based on my experience and understanding of the reactions involved in RPA and DNA synthesis in general.

THE DISCLOSURES OF THE '338 PATENT

The '338 patent describes methods of detecting nucleic acid sequences that use capture of polynucleotide sequences on a solid phase support and non-specific amplification of the captured polynucleotide. I have been informed that the filing date of the first patent application that discloses this combination of steps and from which the '338 patent claims priority is December 21, 1987 (the "filing date").

I understand that I may be asked to testify as to the level of ordinary skill associated with consideration of the '338 Patent. I consider the level of ordinary skill in the art of molecular biology at the filing date of the '338 patent application to have been that of an individual with at least a B.S. degree in the biological sciences and 5 to 7 years relevant post-graduate research experience in molecular biology, which could include research leading to an advanced degree. Such experience would have allowed the individual to develop the skills of a molecular biologist using the techniques of DNA and RNA isolation and characterization, cDNA synthesis, cloning, liquid and solid phase hybridization, isotopic and non-isotopic labeling methods, DNA sequencing methods, and nucleic acid amplification..

Example 6 of the '338 patent describes a method of non-specific enzymatic amplification primed by random hexamer primers and using DNA polymerase. Example 6 suggests that this method could be used to produce an approximately 1,000-fold increase in the level of target DNA.

One of ordinary skill in the art could not have achieved such significant amplification (1000 fold) using random primer amplification of nucleic acid based on the disclosures of the specification of the '338 patent, including Example 6, without first conducting very significant and extensive experimentation to determine the reaction conditions and parameters that would actually allow amplification to occur. Based on the patent's specification, including Example 6, one of ordinary skill in the art could not determine the reaction conditions or parameters that the inventors used or intended to be used in the method suggested in Example 6.

For example, Example 6 suggests the use of Klenow polymerase, an enzyme used to repair or reproduce DNA, in order to achieve amplification. Example 6 does not specify the amount of Klenow polymerase to be used in the random primer amplification process. One of ordinary skill in the art therefore could not determine by reading the patent specification what amount of Klenow polymerase (or any other DNA polymerase) the inventors used or intended for use in the method of Example 6. As of the filing date, one of ordinary skill in the art would not have otherwise known what amount of any DNA polymerase to use in order to achieve exponential amplification using random primers.Other essential information is missing from Example 6. The concentration of hexamer primers and the incubation times and temperatures for DNA synthesis are not disclosed in Example 6. One of ordinary skill in the art therefore could not determine this information by reading the patent specification and would not have otherwise known what concentration of hexamer primers and the incubation times and temperatures to use in order to achieve significantamplification using random primers.

Still other essential information is missing from Example 6. Example 6 requires the use of certain reactants (e.g., deoxynucleotide triphosphates ("dNTP's")) as part of the amplification process. Example 6 does not specify the amount of these reactants to be used. One of ordinary

skill in the art therefore could not determine by reading the patent specification what amount of these reactants the inventors used or intended for use in the method of Example 6. As of the filing date, one of ordinary skill in the art would not have otherwise known what amount of these reactants to use in order to achieve exponential amplification using random primers.

Additionally, Example 6 requires the use of "appropriate buffer" as part of the amplification process. Example 6 does not specify the components or concentration of the buffers to be used. One of ordinary skill in the art therefore could not determine by reading the patent specification what buffer components or concentration the inventors used or intended for use in the method of Example 6. As of the filing date, one of ordinary skill in the art would not have otherwise known what buffer components or concentration to use in order to achieve exponential amplification using random primers.

Reading the patent as a whole, one might generously conclude that the buffer composition and dNTP concentrations listed in Example 5 were intended by the inventors to apply to Example 6. Even if this assumption weremade, essential information about the concentration of Klenow polymerase, the concentration of hexamer primers, and the times and temperature of incubation is still missing from the information disclosed in Example 6.

Furthermore, the buffer described in Example 5 uses concentrations of dNTP reagents that are too high to achieve amplification. Therefore, importing such information from Exhibit 5 does not enable the method of Example 6. Based on my experience and understanding of nucleic acid amplification reactions, one generally uses micromolar concentrations of dNTP reagents. In our work on random primer amplification at Life Technologies, we used dNTP concentrations of 400 micromolar, and we considered those concentrations to be very high. In contrast, Example 5 of the '338 patent describes using almost 100-fold more of these reagents (30 millimolar in Example 5). The buffer described in Example 5 probably would not support polymerization of dNTPs catalyzed by Klenow polymerase because this concentration of dNTPs would chelate all the available magnesium ions that are needed by Klenow polymerase for its enzymatic activity. Also, the pH of the buffer in Example 5 is significantly higher (pH 9.2) than we found optimal

for random priming amplification (pH 6.8, see patent number 5,106,727 at column 10, line 50). (Note that each single digit change in pH represents a 10-fold difference, so a solution of pH 9.2 is over 100-fold more basic than a solution of pH 6.8.)

From the work done by Dr. Hartley, myself and our colleagues, we found that these parameters for reactants and polymerase are critical to obtaining substantial amplification using random primer amplification. In contrast to the method described in Example 6, our methods did not use cycles of denaturation and addition of fresh enzyme. However, I am not aware of any published work in which random primer amplification has been done using repeated denaturations and additions of fresh enzyme as described in Example 6. Moreover, I believe that repeated steps of denaturation at 100 degree Celsius for three minutes, as described in Example 6, would result in chemical damage to the DNA, especially at a pH as high as 9.2, assuming the buffer in Example 5 was used.

When Dr. Hartley and I began working on random priming amplification (in about 1988) it was not at all clear that synthesis of DNA from random primers could lead to significant amplification of DNA targets. Before 1988, those skilled in the art had used random primers and Klenow polymerase for radiolabeling DNA, but not for amplification. When we began our work in about 1988 it was not obvious that random priming would result in exponential amplification and it was certainly not obvious how one would achieve it.

Following considerable experimentation, we succeeded in determining the conditions and parameters that would result in exponential amplification using random primer methods. We then applied for patent protection for our inventions.

Dr. Hartley's application for U.S. Patent No. 5,043,272 was filed on April 27, 1989 and the invention was not publicly disclosed until August 27, 1991. The application which Dr. Hartley and I filed for U.S. Patent No. 5,106,727 was filed on July 13, 1990 and the invention was not publicly disclosed until April 21, 1992.

The U.S. Patent and Trademark Office (USPTO) concluded that Dr. Hartley's and ourmethods were useful, novel, and non-obvious to those skilled in the art in 1989 and 1990, the

time frame when we filed our patent applications. The USPTO also concluded that the description we provided enabled those skilled in the art to practice our invention without undue experimentation.

The process Dr. Hartley and I described in our patent applications is quite different from the one disclosed in Example 6 of the '338 patent. The description in Example 6 lacks any meaningful degree of necessary detail. In contrast, our applications included details on the reaction conditions (e.g., reaction components and concentrations, and incubation times and temperatures) that lead to amplification of the target nucleic acid, information which our later experimentation determined was essential to successful random primer amplification. The amount of information provided in our patent applications indicates how much detailed disclosure is required in order to enable those skilled in the art to achieve substantial amplification using random primers and Klenow polymerase. The difference in the amount and quality of information concerning reaction conditions provided in our patents, compared to the disclosure of Example 6 of the '338 patent, is significant. The degree of detail provided in our patent applications indicates the level of detail that would be necessary to enable those skilled in the art to practice amplification of nucleic acids using random primers.

THE PATENT OWNER'S FAILURE TO ACHIEVE AMPLIFICATION USING RANDOM PRIMERS

As set forth above, I concluded -- based on my prior experience with random primer amplification -- that the disclosures of the '338 patent would not have enabled one of ordinary skill in the art to achieve significantrandom primer amplification without undue experimentation as of the 1987 filing date. I formed the opinions set forth above, above, prior to reviewing any documents produced by the patent owner in discovery in this action.

After I formed my basic opinion, I was provided with certain documents produced by the patent owner in this case.

After reviewing the documents, I determined that the patent owner had tried to achieve exponential amplification using the random primer amplification method described in

Example 6, but that the patent owner's efforts had been unsuccessful. Based on the documents I reviewed, the patent owner apparently abandoned further efforts to determine the conditions necessary to make the method outlined in Example 6 actually work. The patent owner's own unsuccessful attempts to use the method of Example 6 further reinforces my opinion that the method described in Example 6 could not have been used by one skilled in the art to achieve amplification.

For example, I reviewed the monthly report of Scott Decker dated July 17, 1987. There, Dr. Decker reported that he would attempt "random sequence amplification." In subsequent reports, Dr. Decker indicated that preliminary experiments suggested that linear amplification was possible with this method.

I also reviewed Dr. Decker's January 6, 1988 monthly report, in which he summarized results from experiments with random primers. Dr. Decker reported that with repeated cycling, as disclosed in Example 6, "Klenow [polymerase] was found to actually degrade product as well as synthesize — resulting in a *net loss* of the replicated signal after ten rounds of cycling." The method of Example 6, when used by Dr. Decker, actually yielded *less* target rather than more.

In his January 6, 1988 report, Dr. Decker also observed what I stated above: The random priming reaction is "very sensitive to perturbation, that is, changes in experimental conditions such as primer concentration."

Dr. Decker's January 6, 1988 monthly report also stated that when he attempted to improve the random priming method by using a thermostable enzyme (not disclosed in the '338 patent), he still was unable to obtain amplification.

Dr. Decker recognized that "repeated priming on a completely random basis would ultimately lead to an accumulation of shorter and shorter amplified target nucleotide chains." In his January 6, 1988 report, Dr. Decker concluded that the random primer method "was found impractical for exploitation as an amplification scheme."

The conclusion in the first paragraph of Dr. Decker's January 6, 1988 Monthly Report that repeated cycling was found to degrade products is not surprising, particularly if the

temperature cycling regime he is referring to is the one shown at the top of page 123 of his laboratory notebook (experiment recorded October 8, 1987). In this experiment, the reaction was heated to 95 degrees for 2 minutes which could degrade short DNA product to the point where a substantial fraction could no longer be precipitated and detected using his methods (i.e., by using acid). If, the 2 minute "95 degree" incubation was carried out as described on pages 19 and 20 (experiment recorded on September 10, 1987), by using a boiling water bath, then the actual temperature could have been higher than 95 degrees, further increasing the likelihood of DNA degradation. In fact, in Dr. Decker's Monthly Report of July 17, 1987, in paragraph 2, he states the temperature of denaturation as 100 degrees C. In addition, on average the random primers would bind in the center of each target DNA during each cycle. Thus, with each cycle, the product made would be, on average, half the size of the products made in the preceding cycle. The process would rapidly come to a halt as the size of the product diminished. Thus, Dr. Decker's observation that the products became shorter with time is also not unexpected based upon the likely mechanism of synthesis.

I also reviewed other documents reporting on results obtained by the Gene-Trak Amplification and Virology group. The December 1987 report states that "Universal, random primers appear to be of limited use for target amplification." Another document apparently prepared at about the same time states "Random primers have been shown to be useful for *in vitro* replication but not for target amplification through cycling."

I also reviewed subsequent monthly reports from Dr. Scott Decker (e.g., reports for February, March, April 1988). In none of these reports did Dr. Decker report that he had undertaken further work with random primer amplification, suggesting that he abandoned this approach to attempting to amplify target nucleic acids.

In reviewing Kelly Logan's laboratory notebook for the relevant period, I observed that she relied on detecting total incorporation of dNTPs into acid precipitable material (i.e., using a radiolabeled dNTP as a tracer) to measure amplification of template or target DNA. The objective of random primer amplification was not the mere polymerization of dNTP monomers

into polymeric DNA, which was what she measured, but rather producing multiple copies of the target or template DNA sequence. This product was not measured, although Scott Decker in early October 1987 indicated that measurement of such target specific amplification product was attempted (as indicated by references to "dot blot" assays in the Table of Contents and body of the notebook). In the work in which I was involved at Life Technologies to develop random primer amplification, we extensively used "dot blot" assays to track synthesis to target DNA sequences. I found no "dot blot" results among the pages of the notebook provided to me.

I understand that in his deposition in this case, Dr. Decker gave the following testimony::

> Q. Now, we went through in the notes earlier this morning, the monthly reports, if you remember, the January 1988 monthly report that reported the unsuccessful results and conclusions regarding universal or random primer, and that's -- if you remember, that's where Kelley Logan described the problems of perturbation.
>
> A. Yes.
>
> Q. Are the problems of perturbation resolved -- the problems of perturbation in universal or random priming that you detected in your work, are they resolved by any of the disclosures set forth here in example 6?
>
> A. Well, it doesn't mention a problem. If it's been resolved, it doesn't speak to it.
>
> Q. Is there anything about what's set forth in example 6 that you believe would overcome the problems of perturbation that you observed?
>
> A. No, I don't see anything. I mean, obviously, if -- you know, the finickiness of the system was such that it would be necessary to spell it out so somebody else could reproduce it. And that's not in here. So it would probably be very frustrating to try different concentrations.

(Decker Deposition, page 129: line 4 – page 130, line 2.) Dr. Decker's testimony confirms that the disclosures of Example 6 do not provide sufficient information about the conditions for amplification to avoid the perturbation problems that he experienced in his work with random primers. Dr. Decker's testimony further confirms that one skilled in that would have become be very frustrated trying out different conditions in an effort to practice the method described in Example 6.

When the patent owner sought to use the method outlined in Exhibit 6, the patent owner actually obtained *less* of the target nucleic acid, not more. The patent owner then apparently abandoned any further work with the random primer method. The patent owner's own unsuccessful attempts to use the method of Example 6 further reinforces my opinion that the method described in Example 6 could not have been used successfully by one skilled in the art and would not result in exponential amplification.

The results obtained by Scott Decker and Kelly Logan illustrate a fact we discovered at Life Technologies when we began to test random priming as a method of amplifying target DNA. We discovered that, while it was possible to use random primers to achieve target amplification, the reaction parameters needed a lot of adjustment to achieve amplification. Under many conditions we tested, we observed that other unanticipated reactions arose that competed with amplification and that could produce misleading results. We performed a great deal of experimentation to determine the conditions required to produce random priming amplification of target DNA, and the USPTO recognized that we had achieved this result in awarding the random priming patents to Life Technologies years after the first application leading to the '338 patent was filed.

CONCLUSION

My overall conclusion is that the disclosure in Example 6 of the '338 patent would not enable one skilled in the art to achieve exponential amplification using random primers and Klenow polymerase as of the filing date. This conclusion is reinforced by the patent owner's own failed attempts to develop such a method.

August 31_, 2001

Mark S. Berninger